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The Combined use of ACE Inhibitor and AT1 Receptor Blocker on in Albino Rat for Memory Enhancement Activity

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Abstract:
Problem- : Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder that is slow in onset but leads to dementia, unusual behaviour, personality changes and ultimately death. Loss of cholinergic cells, particularly in the basal forebrain, is accompanied by loss of the neurotransmitter acetylcholine. A decrease in acetylcholine in the brain of patients with AD appears to be a critical element in producing dementia. **Approach-** The present work is undertaken to study the combined effect of ACE inhibitor and AT1 receptor blocker on memory function of animals for their establishment in AD. During literature survey I found that ACE inhibitor and AT1 receptor blocker prevents memory impairment, oxidative stress, and also inhibits Anticholinesterase activity. **Finding**- In presents work we find out that the combination of ACE inhibitors and AT1 receptor blocker improve memory more than the individual treatment. Since the causes of some of these medical conditions, such as Alzheimer's, are still unclear, these new research strategies raise expectations for a much needed breakthrough of knowledge into underlying causal mechanisms of inflammation in memory/cognitive loss. **Conclusion-** The findings of this study have shown firstly that for the listed drugs there is a strong association between memory improvement reports. The combination of drugs was evaluated for behavioural assessment was best enhancement property than other ones.

Keywords: Dementia, ACE inhibitors, AT1 receptor blocker, neurode generation.

Introduction: Dementia is a major public health problem affecting around 50 million individuals worldwide. Alzheimer's disease (AD) is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. It was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him. Alzheimer's disease, a chronic and progressive neurodegenerative disease, is a form of dementia. The term dementia is used to describe the symptoms that occur when the brain is affected by specific diseases and conditions, including Alzheimer's disease, vascular dementia, Parkinson's disease, stroke and many other rarer conditions. Dementia is biomedically defined as a progressive and largely

irreversible clinical syndrome that is characterized by a widespread impairment of mental function. Although many people with dementia can retain their previous personality traits and personal attributes well into the disease process, as their condition progresses they can experience language impairment, disorientation, changes in personality, self-neglect, psychiatric symptoms and altered behaviour [1-2].World Health Organization (WHO, 2013) defines mental health as a state of well-being in which the individual realizes his/her abilities, can deal with the normal stresses of life, can work productively, and may contribute to his/her community. This definition of mental health is not only limited to the absence of mental illness but also identifies positive feelings and functioning as critical factors for mental well-being [3].Mental health is a dynamic state of inner stability which enables individuals to use their abilities in harmony with universal values of society. Necessary cognitive and social skills; ability to recognize, express and modulate one's own emotions, as well as identify with others; flexibility and ability to cope with adverse dealing with life and function in social roles; and harmonious association between body and mind represent essential components of mental health which contribute to differ degrees, to the state of internal stability [4].Mental health and mental illness determined by multiple and interacting social, psychological, and biological factors, just as health in general. Various researchers found that mental illness and weak economic status are related. The relationship between poverty and mental disorders is universal and found across societies irrespective of levels of development. Hopelessness, insecurity, rapid social change, the risks of violence and disease are factors responsible for the vulnerability of poor people to mental illnesses [5-6].Mental disorders‘ are manifested by clusters of symptoms or illness experiences, which reflect impaired mental health. Typically, these symptoms are distributed widely in a population, but when they occur in clusters and are associated with impairment in one or more domains of functioning, they are considered to be signs of clinically significant mental disorder [7-8].Depression is a severe problem of every age group in world wild but In Western countries depression and schizophrenia are most often seen by the public as caused by the social environment, In some non-Western cultures, supernatural phenomena, such as witchcraft and possession by evil spirits, are seen as significant causes of mental disorders, although this is uncommon in the West [9].

Material and methods:

Animals: The in-vivo animal experimentation was performed on Swiss albino rat. These rats weighed having 150-200g and use individually for various experiments. Rats were utilize for learn all in-vivo capacity. The animals were domicile to animal quarters previous to testing at temperature of 25±2°C and 50±5% with relative humidity in polypropylene cages through a 12 hours light/dark cycle and allowable free of charge entrance to food and water. The experiments were achieve by subsequent rules and system of CPCSEA

(Committee for the reason of Control and Supervision on Experimental Animals) approved by the IAEC, Bhopal.

In-vivo Pharmacological Screening: The drug powders i.e. enalapril and losartan potassium were evaluated for memory enhancement potentials using the following In-vivo models.

Open-Field Test: After 2 days of habituation, rat received orally water (The first group of animals received as normal control group and the first group of animals received as aged control group. The third group of animals received galantamine (3 mg/kg). The fourth group of animals received 10 mg/kg, body weight enalapril. The fifth group of animals received 20 mg/kg body weight enalapril. The sixth group of animals received 10 mg/kg, body weight of losartan potassium, the seventh group of animals received 20 mg/kg, body weight of losartan potassium, respectively. The eight group of animals received enalapril (10 mg) and losartan potassium (10 mg) to get 20 mg/kg body weight for a period of 4 weeks before behavioural measurement was assessed locomotive activities of rats were tested in open-field on the first day of behavioural test. The effect of drug on rat's loco motor activities was evaluated automatically using an open-field computer-aided controlling system as described in the literatures. The apparatus consists of four metal tanks (30 cm in diameter and 40 cm in height) with a video camera fixed at the top, and the apparatus was illuminated by a light source of 120 Lux on the ceiling. Experiments were performed in a quiet room; four rats were tested simultaneously. Thirty minutes after drug administration, each rats were placed at the centre of the metal tank and allowed to explore freely for 5 min. Then, the distance travelled by rat was measured for 10 min, which was recorded to evaluate the locomotive activity of the rat (Table 1) [12].

Morris Water Maze Test:

Experimentation: After 2 days of habituation, the first group of animals normal control group received normal saline and the second group of animals aged control group. The third group of animals received galantamine (3mg/kg). The fourth group of animals received 10 mg/kg, body weight enalapril. The fifth group of animals received 20 mg/kg body weight enalapril. The sixth group of animal received 10 mg/kg, body weight of losartan potassium, and the seventh group of animals received 20 mg/kg, body weight of losartan potassium respectively. The eight group of animals received enalapril (10 mg) and losartan potassium (10 mg) to get 20 mg/kg body weight for a period of 4 weeks before behavioral measurement was assessed Locomotive activities of rat. The effect of drug on rat loco motor activities was evaluated. Morris water maze tests were carried out on day 2 to day 8 and day 23 to day 25; step- down passive avoidance tests were valued on day 15 to day 16 and day 28, respectively.

Apparatus: The apparatus used for the Acquisition Trials in moris water maze test is a circular water pool (100 cm in diameter and 40 cm in height) with

constant clues external to the maze for spatial orientation of the rat. The water was made opaque by adding black ink to prevent animals from seeing the submerged platform. The water temperature was kept at 24–26◦C during the whole experiment. An invisible platform (6 cm in diameter and 15 cm in height) providing the only escape from water was placed 1.5 cm below the water surface. The pool was divided into four quadrants by a computerized tracking and image analyzer system. Two principal axes of the maze intersect perpendicularly to one another to create an imaginary "+."The end of each line demarcates one of the four cardinal points: north (N), south (S), west (W), and east (E).

Test Procedure. On days 2 to 8 of behavioral measurement, Morris water maze was used to assess the spatial Evidence-Based Complementary and Alternative Medicine 3 reference memory consisting of an acquisition phase and a probe trial. Memory retention of the rat was tested on days 23 to 25. In the acquisition phase, rat was placed in the pool containing platform to adapt to the environment before training. Then rat were subjected to two trials each day for 6 days to find the submerged platform that was located in the center of the SE quadrant of the pool and remained at the same position throughout the whole experiment. Two-day training off our trials contributed to a session. For each trial, the mouse was placed for 15 sec on the platform for learning; then, it was gently released into the pool facing the wall. Four different release points (NE, SE, SW, and NW) were varied randomly for each session. Animals were given a maximum of 60 sec to find the platform. If the mouse failed to find the platform within 60 sec, it was gently guided to the platform and stayed there for 10 sec, and its escape latency was recorded as 60 sec. If an animal found the platform within 60 sec, it was allowed to remain there for 10 sec and was then placed into a cage until next trial. After completion of daily training, the animals were returned to their cages for rest. Escape rate, escape latency, and swimming speed were collected to evaluate the ability of learning and memory function of rat. On the 8th day of behavioral measurement, the spatial probe trials were tested. The platform was removed, and each mouse was placed into the water on the opposite side of the SE quadrant. They were allowed to swim freely for 120 s. The crossing numbers over the position at which the platform had been located, the swimming time, and the swimming distance spent in the target quadrant were recorded as measures for spatial memory. Two weeks after Morris water maze tests, memory retention tests were given. Neither the platform nor the starting point was fixed; rats were released in the opposite quadrant. This training had been performed 2 times each day for 3 days. The average of two trials during a day was determined as escape latency for the purpose of evaluating memory retention abilities of rat.

Table 1 : Distribution of groups of animal

S.No.	Group of Animals	Treatment	Dose
1	G1	Normal Control	Normal Saline
2	G2	Aged group	Normal Saline
3	G3	Piracetam	3.0mg/kg
4	G4	Enalapril	10mg/kg
5	G5	Enalapril	20mg/kg
6	G6	Losartan potassium	10 mg/kg
7	G7	Losartan potassium	20 mg/kg
8	G8	Enalapril : Losartan potassium (10mg:10mg)	20mg/kg

Histopathology studies: When the experiment was performed, rats were decapitated below mild diethyl ether anesthesia. The cerebral tissue (whole-brain) was rapidly dissected and located on ice and weighed. The brain tissue was consequently homogenized in cold 0.1 M phosphate buffer, pH 8.0. The homogenization was performed with about 10-up-and-down strokes at approximately 1200 rev/min in a Teflon glass homogenizer (n=5). The homogenate was centrifuged for 10 min at 3000 rpm to yield and remaining was discarded with low-speed supernatant was kept for previously described assessment. Brain tissue (n=2) from each group were transferred to 10% formal saline for fixation. After which they processed for histological staining of the hippocampus using Haematoxylin and Eosin (H&E) stain (Table 2) [13-14].

Table 2: Drug treatment on brain for histopathology study

S. No.	Group of animals	Treatment	Dose
1	G1	Normal Control	0.9 % Nacl, i.p
2	G5	Enalapril	20 mg/kg
3	G7	Losartan potassium	20 mg/kg
4	G8	Enalapril : Losartan potassium (10mg:10mg)	20 mg/kg

Result and Discussion:

Open-Field Test: The various doses and combination of drugs were evaluated on Mouse Locomotive Activities in the Open Field. As shown in **Table 3** and **Figure 2** no significant effect of same type of drug molecules and its combination on mouse locomotive activities was observed in the open-field test. But galantamine 3 mg/kg reduced the total distance significantly compared with the aged control group ($P< 0.05$). The overall result concluded that the combination of drugs (20 mg/kg) of enalapril and losartan potassium best result than other plants in open field test.

Table 3: Effect of drug molecules on locomotive activities of mice, the total distance travelled by mice was measured after repeated administrations for 4 weeks

S. No.	Group of animals	Treatment	Dose	Total distance (cm)
1	G1	Normal Control	Dist. Water	4110
2	G2	Aged group	Dist. Water	3245
3	G3	Galantamine	3.0 mg/kg	2100
4	G4	Enalapril	10 mg/kg	3443
5	G5	Enalapril	20 mg/kg	3632
6	G6	Losartan potassium	10 mg/kg	3508
7	G7	Losartan potassium	20 mg/kg	3724
8	G8	Enalapril : Losartan potassium (10mg:10mg)	20 mg/kg	3989

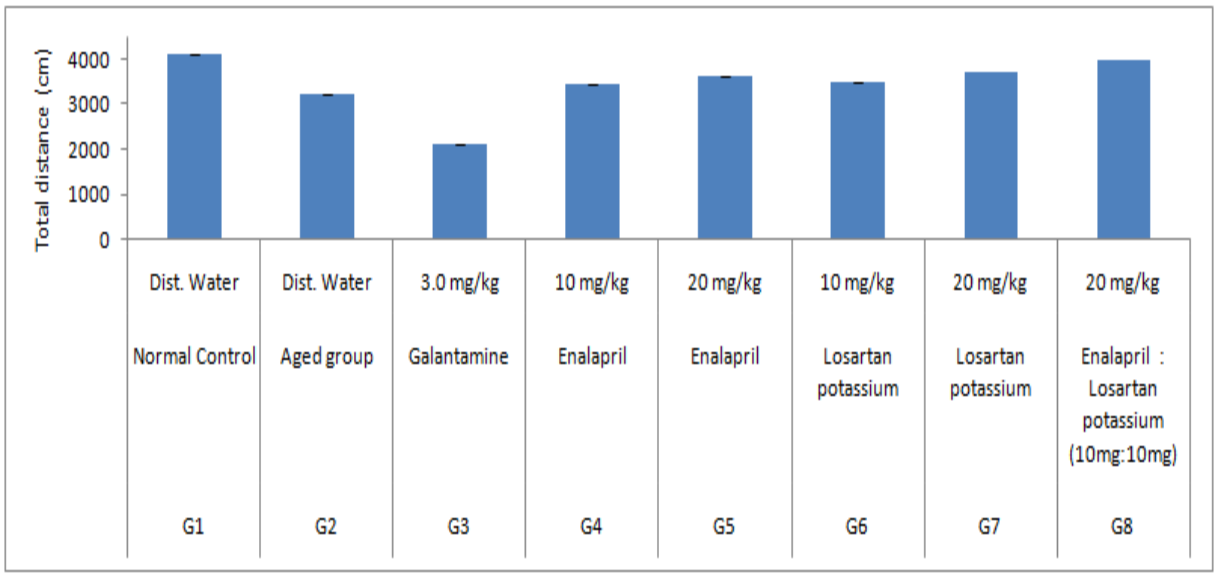
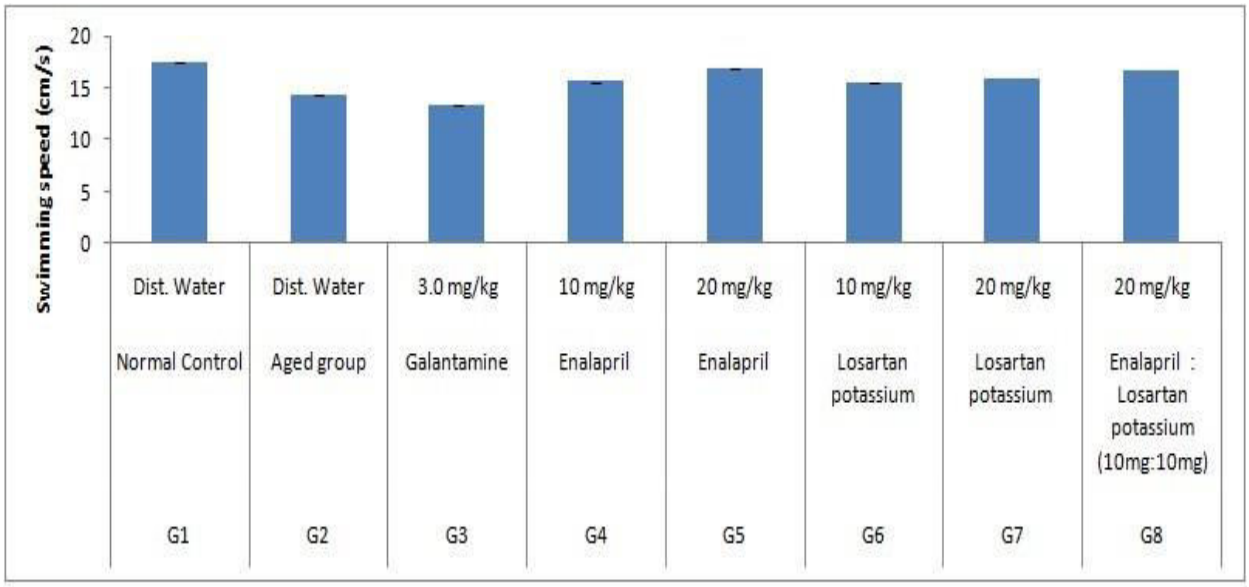


Figure 1: Effect of drug molecules on locomotive activities of mice, the total distance travelled by mice was measured after repeated administrations for 4 weeks

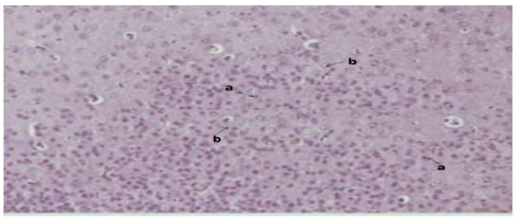
Morris Water Maze Test: The various doses and combination of drugs were evaluated on Mouse Locomotive Activities. As shown in Table 4 and Figure 2 no significant effect of same type of drug molecules on mouse locomotive activities was observed, there were no significant differences on swimming speed in the whole training trials among all the groups. The overall result concluded that the various doses and combination of drugs were assessed best result than other aged group in morris water maze test.

Table 4: Effect of drug molecules on the acquisition phase in MWM tests, Training trials were carried out on day 2 to day 7 of behavioural tests

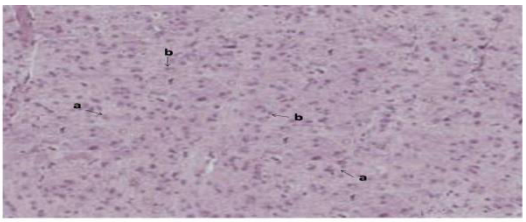
S.No.	Group of animas	Treatment	Dose	Swimming speed (cm/s)
1	G1	NormalControl	Normal Saline	17.5
2	G2	Agedgroup	Normal Saline	14.3
3	G3	Galantamine	3.0mg/kg	13.4
4	G4	Enalapril	10mg/kg	15.6
5	G5	Enalapril	20mg/kg	16.8
6	G6	Losartanpotassium	10mg/kg	15.5
7	G7	Losartanpotassium	20mg/kg	15.9
8	G8	Enalapril:Losartan potassium (10mg:10mg)	20mg/kg	16.7



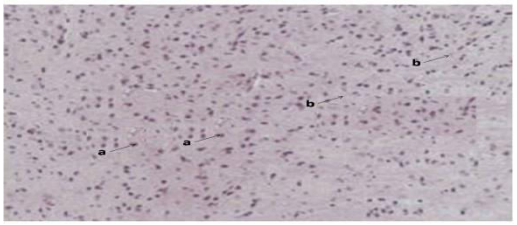
potassium combination was chosen. The photomicrographs of cerebral cortex of mouse were observed after treated for seven days with distilled water (control group). Other ones were G4 Enalapril 10 mg/kg, G5 Enalapril 20 mg/kg, G6 Losartan potassium 10 mg/kg, G7 Losartan potassium 20 mg/kg and G8 Enalapril : Losartan potassium (10mg:10mg) 20 mg/kg. The study was based on normal histology of the cortex and absence of histopathological lesions in brain neurons. Neuronal cells were sketch as dots **Figure 3**(a) (cross section of axon), and glial cells have distinct cell membrane, cytoplasm and nucleus (b) also sketched. These findings indicate that treatment with drug did not cause significant change in the cortex.



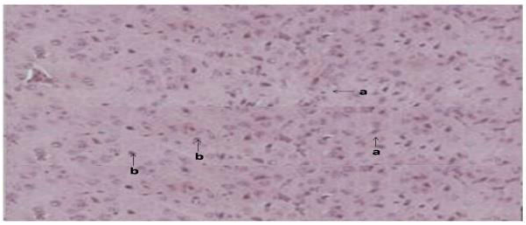
A: G1 (Normal Control)



B: G5 Enalapril 20 mg/kg



C: G7 Losartan potassium 20 mg/kg



D: G9 Enalapril : Losartan potassium (10mg:10mg) 20 mg/kg

Figure 3: Photomicrograph of cerebral cortex of a mouse treated for 7 days with distilled water A: G1, B: G4, C: G5 and D: G6 of drug molecules and its combination

Summary and conclusion: The findings of this study have shown firstly that for the listed drugs there is a strong association between memory improvement reports. The combination of drugs was evaluated for behavioural assessment was best enhancement property than other ones. Open-Field Test of the various doses and combination of drugs were evaluated on rat's locomotive activities in the open field. There is no significant effect of same type of drug molecules and its combination on rat's locomotive activities was observed in the open-field test and Morris water maze test. The overall result concluded that the combination of drugs (20 mg/kg) of enalapril and losartan potassium best result in open field test and Morri's water maze test. The overall result concluded that the various doses and combination of drugs were assessed best result in Morri's water maze test. Aged rats in step-down task in the acquisition trials, the aged control mice revealed marked differences as compared with the normal control mice ($P< 0.05$ or $P< 0.01$). By contrast, the various doses and combination of drugs and galantamine (3 mg/kg) could shorten the latency and the time spent on the electric grid and increase the time spent in the safety zone significantly ($P< 0.01$ or $P< 0.05$). However, no significant differences were observed in all groups on the time in safety zone. The photomicrographs of cerebral cortex of mouse were observed after treated for seven days with distilled water (control group). Other ones were G4 Enalapril 10 mg/kg, G5 Enalapril 20 mg/kg, G6 Losartan potassium 10 mg/kg, G7 Losartan potassium 20 mg/kg and G8 Enalapril : Losartan potassium (10mg:10mg) 20 mg/kg. The study was based on normal histology of the cortex and absence of histopathological lesions in brain neurons. Neuronal cells were sketch as dots (a) (cross section of axon), and glial cells have distinct cell membrane, cytoplasm and nucleus (b) also sketched.

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